Mitochondrial Diseases: Current Treatment Strategies

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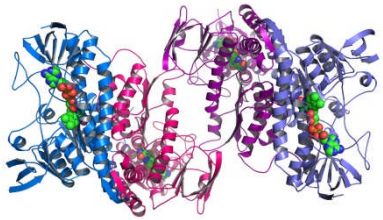
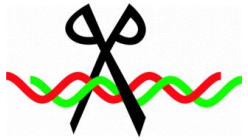
The Lily Foundation Family Weekend 2017

Exciting times!

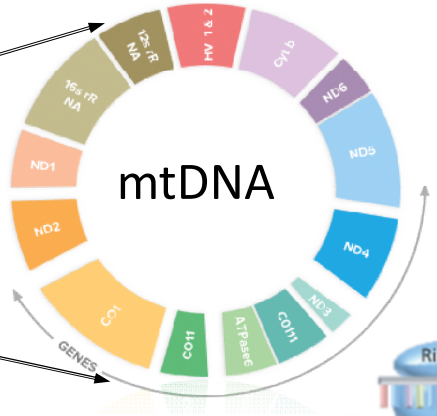


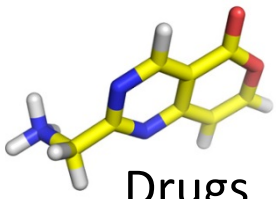
New proteins

Gene transfer

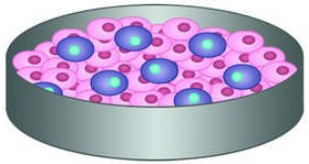


Targeted nucleases





Drugs

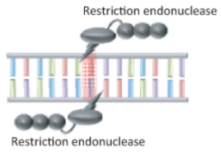
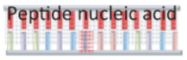
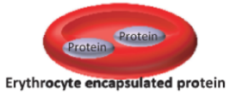
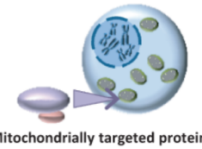
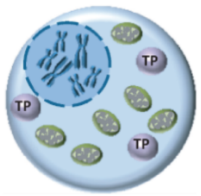


Stem cells

Peptide nucleic acid

tRNA enzymes

Brain. 2016 Jun; 139(6): 1633–1648.

			Examples	Challenges
Manipulating DNA	Mitochondrially-targeted nucleases		Zinc Finger Nucleases Transcription Activator Like Effector Nucleases	Lack of mutation-derived restriction sites for restriction endonucleasses to target Specificity of restriction endonuclease targeting Efficiency of targeting recombinant proteins into cells and mitochondria
	Manipulating mtDNA with peptide nucleic acids			Solubility Efficiency of delivery
	Manipulating tRNA enzymes		Human non-cognate mitochondrial leucyl tRNA synthetase Carboxy-terminal domain of human mitochondrial leucyl tRNA synthetase	Cross reactivity Efficiency of delivery
	Gene transfer using adeno-associated viral vectors		AAV-*ETHE1* (nuclear gene) AAV-*ND4* (mitochondrial gene)	Adeno-associated viruses cannot carry constructs > 5kb Misexpression of the imported gene Efficient delivery to desired cell population Obtaining adequate titres
New protein delivery	Systemic protein delivery		Transfusion of platelets or erythrocyte encapsulated thymidine phosphorylase	Sustaining thymidine phosphorylase levels
	Cellular and mitochondrial protein delivery		Mitochondrially targeted transcription factor A	Over expression is reported to increase mtDNA copy number, mtDNA deletions and respiratory deficiency
Small molecule pharmaceuticals	Manipulating mitochondrial and nuclear DNA		Bezafibrate AICAR Resveratrol PAPR inhibitors Rapamycin Cyclosporin A	Hepatomegaly and abnormal lipid metabolism in animal models Potential hepatic side effects Mild gastrointestinal side effects Mild side effects including fatigue, nausea vomiting and anemia Hyperlipidaemia, poor wound healing and immunosuppression Immunosuppression
Stem cell approaches	Exogenous stem cell therapy for nuclear gene mutations A source of thymidine phorphorylase		Bone marrow and stem cell transplantation	Availability of stem cell transplants Sustaining effect Side effects of myeloablative protocol
	Endogenous stem cells shifting heteroplasmy		Bupivicaine injections Exercise	Finite capacity of repair Limited to patients with isolated mitochondrial myopathies

ClinicalTrials.gov, September 2017

Interventional Studies | Mitochondrial Disease | Phase 2: **15 active studies**

Study Title	Conditions	Interventions	Study Type	Phase	Number Enrolled
Mitochondria and Chronic Kidney Disease	Hemodialysis-Induced Symptom; Mitochondrial Diseases	Drug: Icatibant; Drug: Placebo	Interventional	Phase 2	11
Safety and Efficacy Study of Gene Therapy for The Treatment of Leber's Hereditary Optic Neuropathy	Leber Hereditary Optic Neuropathy	Drug: rAAV2-ND4; Drug: normal saline	Interventional	Phase 2 / Phase 3	48
Open-Label Extension Trial to Characterize the Long-term Safety and Tolerability of Elamipretide in Subjects With Genetically Confirmed Primary Mitochondrial Disease (PMD)	Primary Mitochondrial Disease	Drug: elamipretide	Interventional	Phase 2	36
The KHENERGY Study	Mitochondrial Diseases; Mitochondrial Myopathies; Mitochondrial Encephalomyopathies; MELAS; MIDD	Drug: KH176; Drug: placebo	Interventional	Phase 2	20
A Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects With Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study	Primary Mitochondrial Disease	Drug: Elamipretide; Drug: Placebo	Interventional	Phase 2	30
A Study Investigating the Safety, Tolerability, and Efficacy of Elamipretide (MTP-131) Topical Ophthalmic Solution for the Treatment of Leber's Hereditary Optic Neuropathy	Leber's Hereditary Optic Neuropathy	Drug: elamipretide (MTP-131) 1% topical ophthalmic solution; Drug: Vehicle topical ophthalmic solution	Interventional	Phase 2	12
(+) Epicatechin to Treat Friedreich's Ataxia	Friedreich's Ataxia	Drug: (+)-Epicatechin	Interventional	Phase 2	10
A Study of Bezafibrate in Mitochondrial Myopathy	Mitochondrial Diseases	Drug: Bezafibrate	Interventional	Phase 2	10
Long-Term Safety and Efficacy Evaluation of EPI-743 in Children With Leigh Syndrome	Leigh Syndrome	Drug: EPI-743	Interventional	Phase 2	31
RTA 408 Capsules in Patients With Friedreich's Ataxia - MOXIe	Friedreich Ataxia	Drug: Omaveloxolone Capsules, 2.5 mg; Drug: Omaveloxolone Capsules, 5 mg; Drug: Omaveloxolone Capsules, 10 mg; Drug: Placebo; Drug: Omaveloxolone Capsules, 20 mg; Drug: Omaveloxolone Capsules, 40 mg; Drug: Omaveloxolone Capsules, 80 mg; Drug: Omaveloxolone Capsules, 160 mg; Drug: Omaveloxolone Capsules, 300 mg; Drug: Omaveloxolone Capsules, 150 mg	Interventional	Phase 2	172
RTA 408 Capsules in Patients With Mitochondrial Myopathy - MOTOR	Mitochondrial Myopathies	Drug: Omaveloxolone capsules, 2.5 mg; Drug: omaveloxolone capsules, 5 mg; Drug: omaveloxolone capsules, 10 mg; Drug: Placebo capsules; Drug: omaveloxolone capsules, 20 mg; Drug: omaveloxolone capsules, TBD mg; Drug: omaveloxolone capsules, 40 mg; Drug: omaveloxolone capsules, 80 mg; Drug: omaveloxolone capsules, 160 mg	Interventional	Phase 2	100
Safety Evaluation of Gene Therapy in Leber Hereditary Optic Neuropathy (LHON) Patients	Leber Hereditary Optic Neuropathy	Genetic: GS010	Interventional	Phase 1 / Phase 2	21
EPI-743 for Metabolism or Mitochondrial Disorders	Undiagnosed Diseases; Metabolic Disease; Neurology; Myoptahy; Oxidation/Reduction; Mitochondrial Disorders	Drug: EPI-743	Interventional	Phase 2	20
Effect of Nicotinamide in Friedreich's Ataxia	Neurodegenerative Disorders	Drug: nicotinamide	Interventional	Phase 2	40
EPI-743 for Mitochondrial Respiratory Chain Diseases	Mitochondrial Diseases	Drug: EPI-743	Interventional	Phase 2	87

What about now!

What is a treatment?

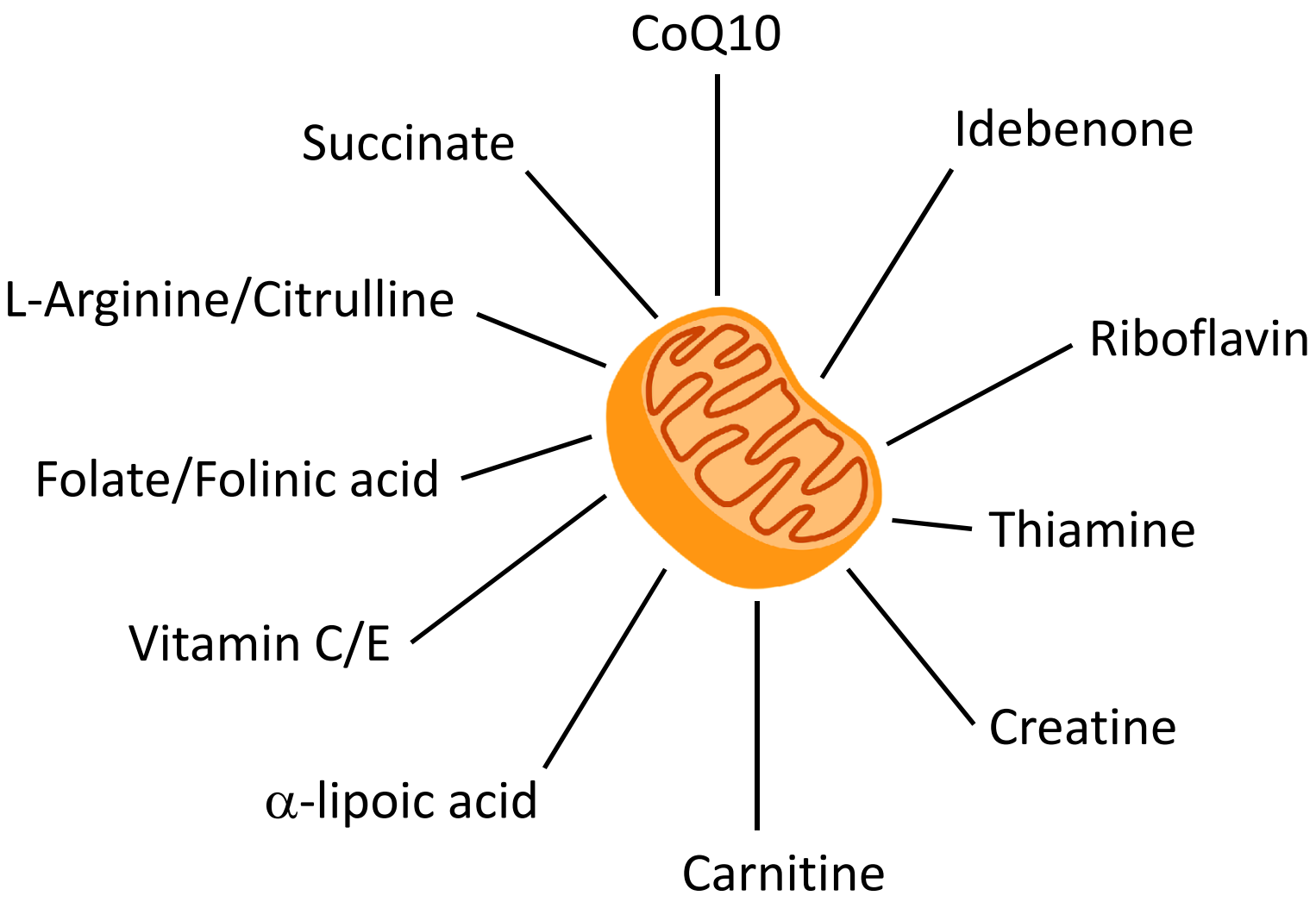
Anything that improves quality of life

Overview

- Pharmacological agents, vitamins and related substances
  - Underlying disease versus symptoms
  - Specific treatable clinical syndromes
- Exercise and dietary modification
- Health surveillance and monitoring
- Emergency plans and acute management

Pharmacological agents, vitamins and related substances

Vitamins, cofactors and food supplements



Pharmacological agents and vitamins

Cochrane Database of Systematic Reviews

Treatment for mitochondrial disorders (2012)

- 1335 abstracts (1966-2012)
- 12 trials well designed:
  - Coenzyme Q10
  - Creatine
  - Creatine/Q10/lipoic acid combo
  - Dichloroacetate
  - Dimethylglycine
  - Cysteine
- No evidence supporting use of any intervention in mitochondrial disorders

Randomised, double-blinded, placebo-controlled clinical trials in mitochondrial disease

Treatment	Disease	No. of participants	Type of trial	Outcome	References
CoQ_{10}	MELAS, PEO, complex I deficiency, NARP, LHON	30	Randomized, placebo-controlled, double-blind crossover	Serum CoQ_{10} increased, lactate levels decreased after 1 min of cycle ergometry, but no significant change in other endpoints	Glover *et al.*, 2010
Creatine	MELAS and MM	7	Randomized, placebo-controlled, double-blind crossover	Increased handgrip strength, NIDT and post-exercise lactate	Tarnopolsky *et al.*, 1997
	CPEO and MM	16	Randomized, placebo-controlled, double-blind crossover	No effect	Klopstock *et al.*, 2000
	CPEO and KSS	15	Randomised, placebo-controlled crossover	No effect	Kornblum *et al.*, 2005
DCA	MM, CPEO, KSS, Leigh syndrome, MELAS	11	Randomised, placebo-controlled, double-blind crossover	Decreased blood lactate, pyruvate and alanine at rest and post-exercise, some improvements in brain MRS	De Stefano *et al.*, 1995
	CPEO, MERRF, MM	8	Randomized, placebo-controlled, double-blind crossover	Decreased resting and exercise lactate and pyruvate	Vissing *et al.*, 2001
	Mitochondrial RC disorders	9	Randomized, placebo-controlled, double-blind crossover	Decreased blood lactate levels during exercise	Duncan *et al.*, 2004
	MELAS m.3243A>G	30	Randomized, placebo-controlled crossover	No effect. Study terminated due to side effects (peripheral neuropathy)	Kaufmann *et al.*, 2006
	Congenital lactic acidosis	43	Randomized, double-blinded, placebo-controlled parallel group	Reduced blood lactate levels post high carbohydrate meal	Stacpoole *et al.*, 2006
Dimethylglycine	SLSJ-COX	5	Randomized, placebo-controlled crossover	No effect	Liet *et al.*, 2003
Whey-based cysteine	PEO	13	Randomized, placebo-controlled, double-blind crossover	Glutathione levels increased. Advanced oxidation protein products and ferric-reducing antioxidant power increased	Mancuso *et al.*, 2010
Combination therapy (creatine, α-lipoic acid and CoQ_{10})	CPEO, KSS, MELAS, MNGIE, MM	16	Randomized, placebo-controlled, double-blind crossover	Decreased plasma lactate, slower disease progression (measured by peak angle dorsiflexion strength).	Rodriguez *et al.*, 2007

CPEO, chronicprogressive external ophthalmoplegia; MERRF, myoclonic epilepsy, ragged red fibres; NIDT, non-ischaemic, isometric, dorsiflexion torque; SLSJ-COX, Saguenay-Lac-Saint-Jean COX deficiency.

Kanabus. Br J Pharmacol. 2014 Apr; 171(8): 1798–1817.

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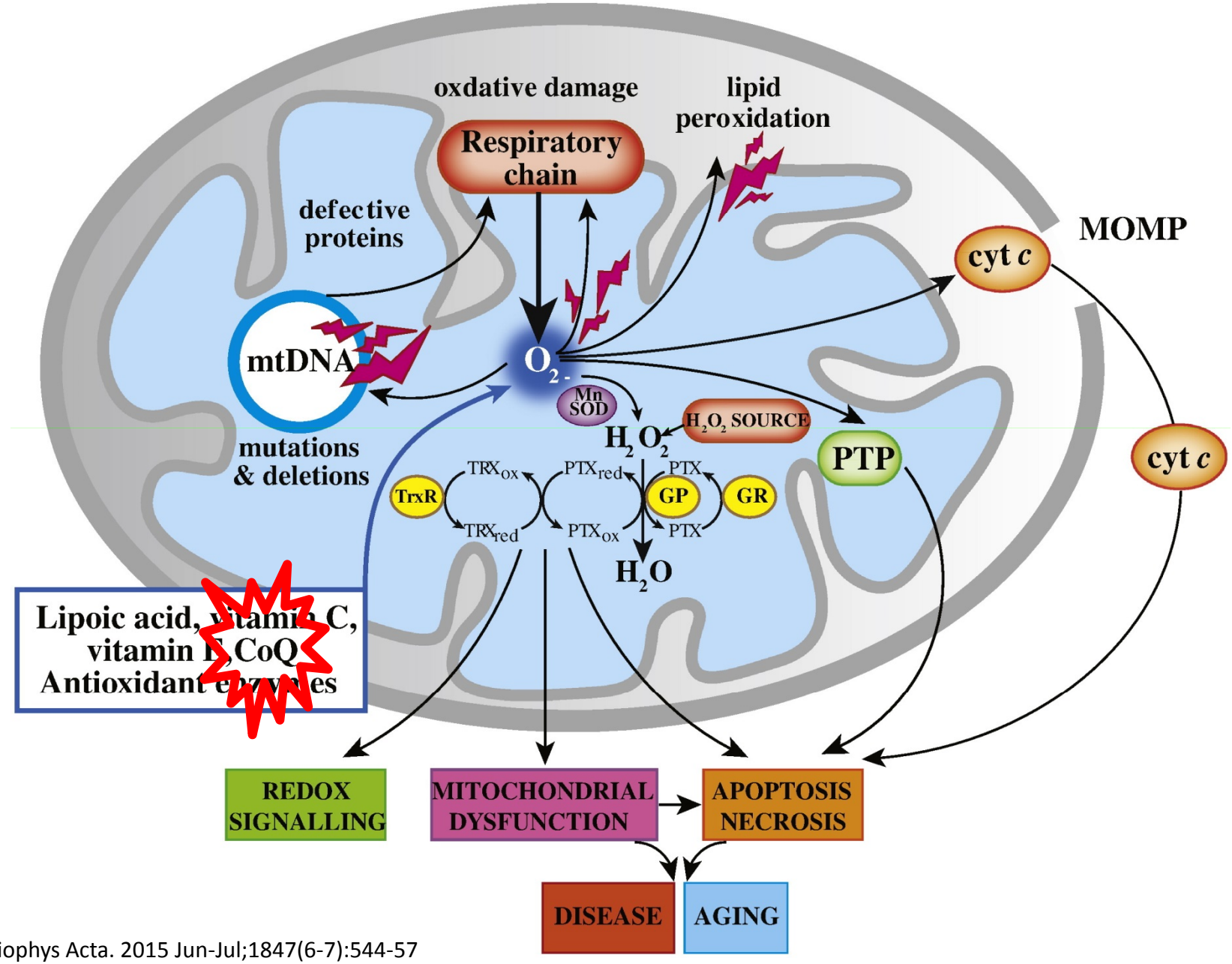
Reactive oxygen species and their detoxification



Biochim Biophys Acta. 2015 Jun-Jul;1847(6-7):544-57

Mitochondrial diseases with specific treatment options

Affected pathway	Clinical syndrome	Affected gene(s)	Clinical phenotype	Therapeutic substance	Treatment response
Primary disorders of mitochondrial vitamin cofactor metabolism	Brown-Vialetto-Van Laere syndrome / Fazio-Londe disease	*SLC52A2*, *SLC52A3*, *(SLC52A1)*[a]	Sensorineural hearing loss, cranial nerve palsies	Riboflavin (oral: 10–50 mg/kg/day)[b]	Generally good
	Biotin-thiamine-responsive basal ganglia disease	*SLC19A3*	Episodic encephalopathy, dystonia, seizures	Thiamine (oral: 10–20 mg/kg/day), biotin (oral: 10–15 mg/kg/day)[c]	Generally good
	Biotinidase deficiency	*BTD*	Dermatitis, muscular hypotonia, developmental regression	Biotin (oral: 5–10 mg/kg/day)[d]	Generally good
	Holocarboxylase synthetase deficiency	*HLCS*	Skin lesions, metabolic acidosis, seizures, developmental delay	Biotin (oral: 10–20 mg/kg/day)[e]	Variable but generally good
	Thiamine pyrophosphokinase deficiency	*TPK1*	Episodic encephalopathy, dystonia, spasticity	Thiamine (oral: ~20 mg/kg/day)[f]	Variable (<10 patients treated so far)
Disorders with indirect response to mitochondrial vitamin cofactor supplementation	ACAD9 deficiency	*ACAD9*	Encephalopathy, myopathy, hypertrophic cardiomyopathy	Riboflavin (oral: 10–20 mg/kg/day)[g]	Variable
	Multiple acyl-CoA dehydrogenase deficiency	*ETFA*, *ETFB*, *ETFDH*, *SLC25A32*, *FLAD1*	Early childhood multisystem disease or late-onset form with muscle weakness, hepatopathy, etc.	Riboflavin (oral: ~10 mg/kg/day)[h]	Generally good
	Thiamine-responsive pyruvate dehydrogenase deficiency	*PDHA1*	Neonatal lactic acidosis, seizures, developmental regression, spasticity	Thiamine (oral: 30–40 mg/kg/day)[i]	Variable
Disorders of mitochondrial non-vitamin cofactor metabolism	Coenzyme Q_{10} deficiency	*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ7*, *ADCK3*, *ADCK4*, *COQ9*	Variable phenotypes, ranging from adult-onset myopathy to fatal neonatal presentations	Coenzyme Q_{10} (oral: 10–30 mg/kg/day)[j]	Highly variable depending on the underlying defect
Disorders of mitochondrial inorganic cofactor metabolism	Cytochrome c oxidase deficiency	*SCO2*, *COA6*	Infantile encephalocardiomyopathy	Copper–histidine (dose unclear; subcutaneous injections of up to 500 μg daily were suggested)[k]	Unclear, only one *SCO2* patient treated; only *in vitro* evidence for *COA6*
	Molybdenum cofactor deficiency	*MOCS1*, *MOCS2*, *GPHN*	Infantile-onset epileptic encephalopathy, progressive brain damage	Cyclic pyranopterin monophosphate (intravenous: 80–320 μg/kg/day)[l]	Generally good in MoCD type A patients
'Inhibitors' of mitochondrial metabolism	3-Hydroxyisobutyryl-CoA hydrolase deficiency	*HIBCH*	Infantile Leigh-like phenotype	Valine-restricted diet[m]	Unclear, only few patients treated
	Enoyl-CoA hydratase deficiency	*ECHS1*	Infantile Leigh-like phenotype	Valine-restricted diet[n]	Unclear, only few patients treated so far
	Thioredoxin 2 deficiency	*TXN2*	Cerebellar atrophy, dystonia, seizures, peripheral neuropathy	Antioxidant treatment (e.g. Idebenone up to 20 mg/kg/day)[o]	Apparently good (only one patient reported)
	Ethylmalonic encephalopathy	*ETHE1*	Severe, multisystem infantile disorder	Metronidazole, *N*-acetyl cysteine as glutathione precursor, liver transplantation[p]	Variable

Brain. 2017 Feb;140(Pt 2):e11.

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	Ethylmalonic encephalopathy	*ETHE1*	Severe, multisystem infantile disorder	Metronidazole, *N*-acetyl cysteine as glutathione precursor, liver transplantation[p]	Variable

Mitochondrial diseases with spontaneous recovery

"Benign" reversible mitochondrial myopathy

Acute liver failure in infancy (TRMU)

Brain. 2017 Feb;140(Pt 2):e11.

Exercise and diet

Exercise

- Important for general fitness : exercises muscles and keeps heart and circulation healthy
- If you become unfit can adversely affect muscles
- In many patients' muscles there is a mixture of good and bad mitochondria; the hope is that exercise can increase the good mitochondria, boosting the level of ATP so avoiding symptoms
- This remains a theory and there are large trials looking at this idea
- Current advice is to exercise regularly at a level that is comfortable, but without pushing yourself to the point that the muscles become painful

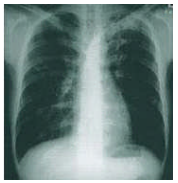
Dietary modification

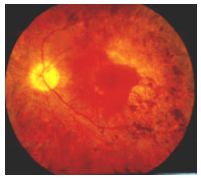
- Ketogenic (high fat / low carbohydrate) diet: promotes formation of ketone bodies (via FAO)
- Ketone bodies:
  - Alternative energy source for brain, heart and muscle
  - Associated with ↑OXPHOS gene expression (akin to starvation)
  - Possibly stimulate mitochondrial biogenesis
- No randomized, double-blinded trial data
- PDH deficiency
- Seizures
- Dietetic supervision!

Health surveillance and monitoring

Clinical variability

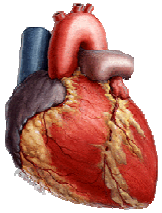
Respiratory Failure

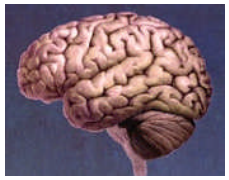




Ptosis
Optic Atrophy
Retinitis Pigmentosa
Cataracts

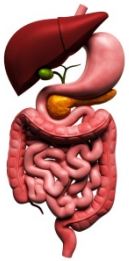
Cardiomyopathy
Conduction Defects

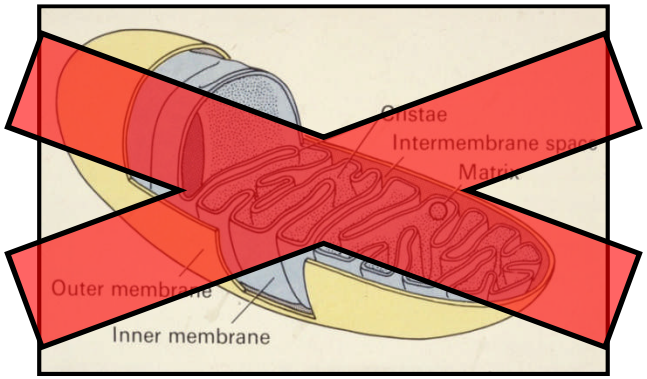


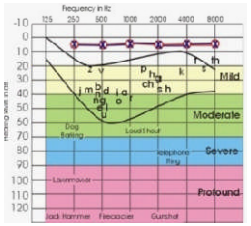


Stroke / Seizures
Developmental Delay
Movement Disorders

Liver /
Renal
Failure
Dysphagia
Gut
dysmotility

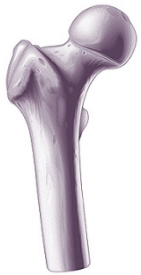


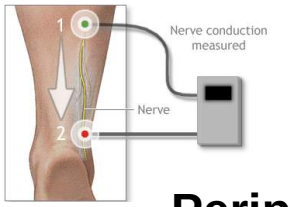




Deafness

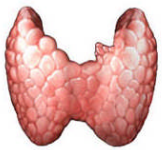
Short stature
Marrow Failure





Peripheral neuropathy

Diabetes

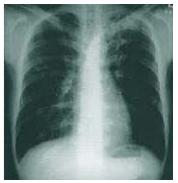


Hypothyroidism

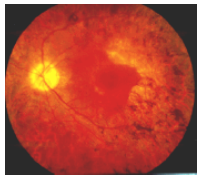
Fatigue
Myopathy
Exercise intolerance

Surveillance enables early treatment

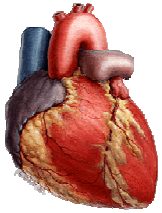
Ventilator support

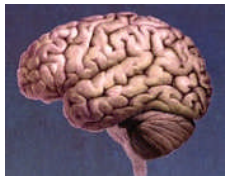


Photocoagulation
Ptosis surgery
Eyelid props
Cataract surgery
Prisms



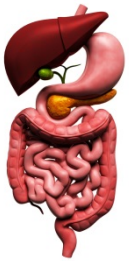
Drugs
PPM
ICD
Ablation
Transplant

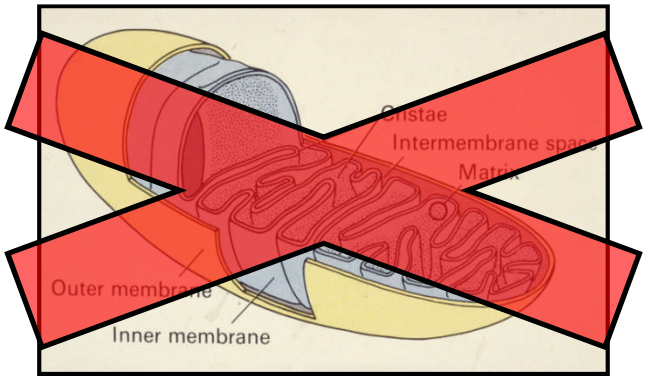


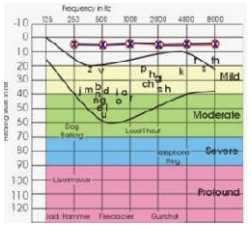


AEDs
Botox and drugs
Tendon release
DBS

Dietician
SALT
PEG
Laxatives
Microbiome
Dialysis
Transplant

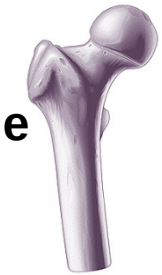


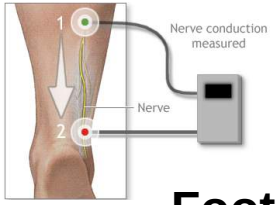




Hearing aids
Cochlear implants

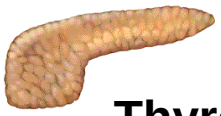
Growth hormone
Transfusion
Transplant



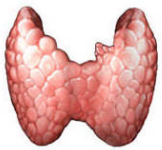


Foot care
Orthotics
Surgery

Diet
Drugs
Insulin
Enzymes



Thyroxine
Radioiodine
Surgery



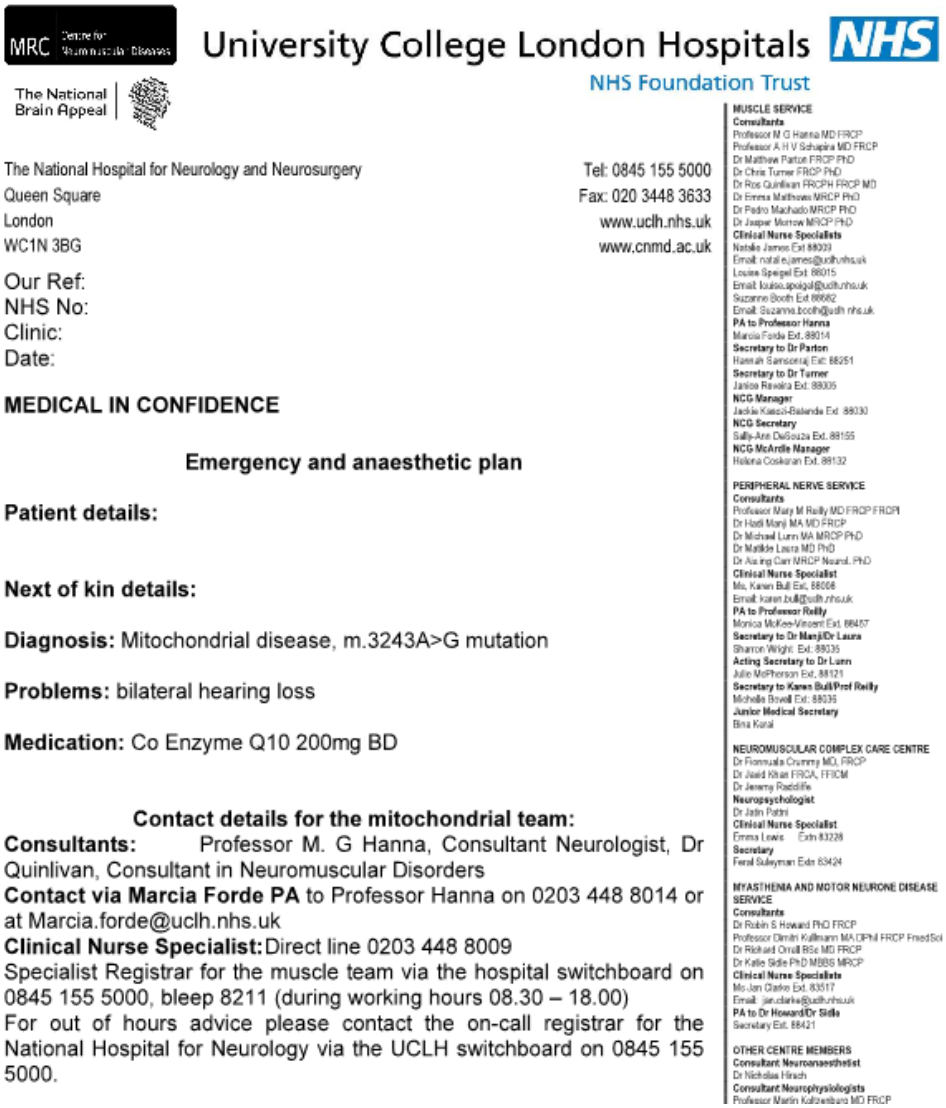
CoQ10/exercise
PT/OT/exercise
Energy conservation

Guidelines - http://mitochondrialdisease.nhs.uk

For patients and professionals…

Emergency plans and acute management

Emergency plan



University College London Hospitals NHS
NHS Foundation Trust

The National Brain Appeal

The National Hospital for Neurology and Neurosurgery
Queen Square
London
WC1N 3BG

Tel: 0845 155 5000
Fax: 020 3448 3633
www.uclh.nhs.uk
www.cnmd.ac.uk

Our Ref:
NHS No:
Clinic:
Date:

MEDICAL IN CONFIDENCE

Emergency and anaesthetic plan

Patient details:

Next of kin details:

Diagnosis: Mitochondrial disease, m.3243A>G mutation

Problems: bilateral hearing loss

Medication: Co Enzyme Q10 200mg BD

Contact details for the mitochondrial team:

Consultants: Professor M. G Hanna, Consultant Neurologist, Dr Quinlivan, Consultant in Neuromuscular Disorders
Contact via Marcia Forde PA to Professor Hanna on 0203 448 8014 or at Marcia.forde@uclh.nhs.uk
Clinical Nurse Specialist: Direct line 0203 448 8009
Specialist Registrar for the muscle team via the hospital switchboard on 0845 155 5000, bleep 8211 (during working hours 08.30 – 18.00)
For out of hours advice please contact the on-call registrar for the National Hospital for Neurology via the UCLH switchboard on 0845 155 5000.

Acute management

- Education and early recognition of warning signs:
  - Nausea and vomiting
  - Confusion, sleepiness or irritability
  - Weakness, numbness or speech problems
  - Visual or hearing disturbance
  - Seizures
  - Severe headaches
  - Sudden bowel problems

Acute management

- Seek medical attention early (GP or A&E)
- Ensure any infection treated and well hydrated
- Review medications
- Admit to hospital for:
  - Seizure control
  - Intravenous fluids (dextrose)
  - Intravenous antibiotics
  - Correction of acidosis

Summary

- Lots of exciting treatments in pipeline – but let's not forget there's lots we can do now!

- No clear evidence from trials for current pharmacological agents, vitamins and cofactors – apart from specific scenarios

- Surveillance and treatment of complications and recognition of warning signs crucial

Thank you